Risk of chronic kidney disease after cancer nephrectomy

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Abstract | The incidence of early stage renal cell carcinoma (RCC) is increasing and observational studies have shown equivalent oncological outcomes of partial versus radical nephrectomy for stage I tumours. Population studies suggest that compared with radical nephrectomy, partial nephrectomy is associated with decreased mortality and a lower rate of postoperative decline in kidney function. However, rates of chronic kidney disease (CKD) in patients who have undergone nephrectomy might be higher than in the general population. The risks of new-onset or accelerated CKD and worsened survival after nephrectomy might be linked, as kidney insufficiency is a risk factor for cardiovascular disease and mortality. Nephron-sparing approaches have, therefore, been proposed as the standard of care for patients with type 1a tumours and as a viable option for those with type 1b tumours. However, prospective data on the incidence of *de novo* and accelerated CKD after cancer nephrectomy is lacking, and the only randomized trial to date was closed prematurely. Intrinsic abnormalities in non-neoplastic kidney parenchyma and comorbid conditions (including diabetes mellitus and hypertension) might increase the risks of CKD and RCC. More research is needed to better understand the risk of CKD post-nephrectomy, to develop and validate predictive scores for risk-stratification, and to optimize patient management.

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Introduction

Renal cell carcinoma (RCC) is the third most common genitourinary malignancy in the USA (after prostate and bladder cancers), and the seventh and the ninth leading cause of any cancer in men and in women, respectively.[1] In 2012, >64,000 people in the USA were diagnosed with cancer of the kidney—predominantly RCC—and approximately 13,000 associated deaths were reported.[2] The incidence of RCC has been increasing steadily for the past two decades, largely due to advancements in diagnostic technology and easier access to abdominal imaging for unrelated conditions. As a result, the size and the stage of tumours at the time of diagnosis has decreased.[3] Incidental asymptomatic stage I tumours (type 1a [T1a] and type 1b [T1b], tumour diameters ≤4 cm and ≤7cm, respectively) now account for more than half of newly diagnosed RCCs.[4,5]

Surgical resection remains the gold-standard treatment for RCC. Although very promising, alternative management strategies, such as ablation and active surveillance, require longer term follow-up duration and are still under investigation. For decades radical nephrectomy was the primary treatment for kidney tumours regardless of their size,[6] whereas partial nephrectomy was reserved for patients with imperative indications, such as a solitary kidney, bilateral renal tumours, or pre-existing renal disease.[7] However, the management of small localized renal tumours has evolved substantially over time, with an increasing emphasis on preservation of renal volume and function. In the past decade, several studies have demonstrated oncological equivalence of partial nephrectomy compared with radical nephrectomy for stage I lesions.[8–12] Although 5-year cancer-specific survival is >90%, regardless of surgical approach,[13,14] emerging evidence favours partial nephrectomy over radical nephrectomy because the less-invasive surgery is associated with a lower incidence of postoperative chronic kidney disease (CKD) and a reduction in associated adverse cardiovascular outcomes. Partial nephrectomy has, therefore, become the preferred nephron-sparing surgery in elective settings and is now offered to patients with unilateral small renal masses and normal contralateral kidney function. In 2009, the American Urological Association published clinical guidelines that suggested partial nephrectomy as the standard of care for T1a RCC and as a viable option for T1b RCC.[15] Similar guidelines were later endorsed by the European Association of Urology.[16]

In this Review, we describe the available evidence and ongoing controversy regarding the potential benefits of partial versus radical nephrectomy for small renal masses, in particular T1a lesions. We also discuss the risk of *de novo* kidney disease or acceleration of CKD progression post-nephrectomy, potential factors that might influence patient prognosis after this surgery, and the need for further research to better understand the natural history and progression of CKD after nephrectomy.

Competing interests
K. Kalantar-Zadeh declares associations with the following companies: Abbott, DaVita, Fresenius, Genzyme, and Shire. See the article online for full details of the relationships. The other authors declare no competing interests.

Key points

- Partial nephrectomy preserves renal function in the long term and is currently the preferred standard of care for small renal cell carcinomas (RCCs)
- Evidence for a beneficial effect of nephron-sparing approaches versus radical nephrectomy for RCC on long-term chronic kidney disease (CKD)-associated morbidity and overall survival is inconclusive and controversial
- The quantity and integrity of the preserved renal parenchyma after nephrectomy are important predictors of long-term renal outcomes
- Renal tumours and CKD share intrinsic kidney risk factors and systemic comorbidities and a bi-directional relationship between RCC and CKD has been proposed
- Further research is needed to quantify the perioperative risks and potential long-term benefits of nephron-sparing surgery for RCC
- A prediction model to identify patients at risk of oncological and nononcological morbidity and mortality after nephrectomy would help personalize the management of patients with small RCCs

Nephrectomy and CKD

CKD is now recognized as a public health problem worldwide. The disease is defined as kidney damage for >3 months (confirmed by pathologic abnormalities in biopsy samples or by markers of kidney damage such as proteinuria) with or without changes in glomerular filtration rate (GFR), or GFR <60 ml/min/1.73 m^2 for >3 months with or without kidney damage.[17] The incidence and prevalence of CKD have been steadily increasing worldwide, both in developed countries and in large emerging economies, such as India and China.[18] The Center for Disease Control and Prevention estimated that >10% of the US population—or >20 million people aged ≥20 years in the USA—had CKD in 2010.[19]

Radical nephrectomy for RCC was first described in 1969.[6] The procedure (as originally described) involves complete resection of the kidney, adrenal gland, and tumour within the Gerota's fascia as well as local lymphadenectomy and results in excellent local tumour control.[6] In the past, urologists advised their patients that the impact of radical nephrectomy on kidney function was minimal, based on data extrapolated from several large cohort studies of kidney donors. These studies showed that after unilateral radical nephrectomy for transplant donation, normal renal function could be maintained by a solitary kidney at long-term follow up.[20–22] Radical nephrectomy was, therefore, considered the standard of care for localized renal masses. However, the typical transplant donor population differs significantly from patients with RCC, who tend to be much older than healthy screened kidney donors, and often have pre-existing kidney diseases and risk factors (such as diabetes mellitus, hypertension, smoking, and obesity) that might predispose them towards developing both kidney tumours and kidney damage.[23,24]

Single-centre retrospective studies

Evidence that radical nephrectomy, compared with partial nephrectomy, for the treatment of small localized renal masses could lead to a substantial decline in kidney function emerged in the mid-1990s (Tables 1 and 2). Butler *et al.*[25] were among the first to report an adverse effect of radical nephrectomy on estimated glomerular filtration rate (eGFR). They found that patients with RCC who underwent radical nephrectomy had significantly higher postoperative mean serum creatinine levels than those who underwent partial nephrectomy. However, the study was limited by a small sample size ($n = 88$).

Data from larger single-centre retrospective studies of patients who underwent partial or radical nephrectomy for T1a RCC were reported subsequently. In 2000, a cohort study of patients with unilateral RCC and a normal contralateral kidney who underwent either partial ($n = 164$) or radical nephrectomy ($n = 164$) between 1966 and 1969 was published. Patients were case-matched for pathology, tumour size, age, sex, and year of surgery. At 10-year follow-up, those who underwent radical nephrectomy had a significantly higher estimated cumulative incidence of renal insufficiency (defined as serum creatinine level >176.8 μmol/l) than those who underwent partial nephrectomy (22.4% versus 11.6%, hazard ratio [HR] 3.7, 95% CI 1.2–11.2).[14] A study that included 290 patients from the Memorial Sloan–Kettering Cancer Center (MSKCC), New York, USA, with a median follow-up of 25 months reported similar findings. At baseline the radical and partial nephrectomy groups had similar mean preoperative serum creatinine levels (88.4 μmol/l and 86.63 μmol/l, respectively) and were comparable in terms of risk factors for renal insufficiency, including diabetes mellitus, hypertension, age, American Society of Anaesthesiologists score for physical status,[26] and smoking status. At the end of the follow-up period, the mean postoperative serum creatinine level was significantly higher in the radical nephrectomy group than in the partial nephrectomy group (132.6 μmol/l versus 88.4 μmol/l, $P < 0.001$).[27]

Serum creatinine level alone is not a good index of renal function because of high day-to-day variability and inaccuracy at extremes of age and body habitus, such as obesity and amputation.[28] However, the protective effect of nephron-sparing surgery on long-term renal function has been further confirmed by studies that used estimated GFR (eGFR) as a measure of renal function. In a retrospective cohort of 662 patients from MSKCC with normal baseline serum creatinine levels who underwent elective partial or radical nephrectomy for a solitary T1a RCC between 1989 and 2005, 26% of participants had CKD defined as eGFR <60 ml/min/1.73 m^2 (estimated using the abbreviated Modification of Diet in Renal Disease equation[29]) before surgery.[30] The impact of partial versus radical nephrectomy on the risk of CKD was examined using two different definitions of the disease: eGFR <60 ml/min/1.73 m^2 or eGFR <45 ml/min/1.73 m^2. The 3-year postoperative probability of freedom from new onset of eGFR <60 ml/min/1.73 m^2 was 80% after partial nephrectomy versus 35% after radical nephrectomy ($P < 0.0001$). Furthermore, probability for eGFR <45 ml/min/1.73 m^2 was 95% after partial nephrectomy versus 64% after radical nephrectomy ($P < 0.0001$). Multivariable analysis showed that radical nephrectomy was an independent risk factor for the development of new onset CKD (HR 3.82, 95% CI

Table 1 | Single-centre studies examining outcomes following partial versus radical nephrectomy

Study [population]	*n*		Results	Limitations
	PN	RN		
Butler *et al.* (1995)[25] [Cleveland Clinic registry 1975–1992, T1a tumours]	46	42	Similar cancer-specific 5-year survival in PN (100%) and RN (97%) groups Significant increase in mean SCr levels after surgery in RN group only	Single-centre, retrospective study
Lau *et al.* (2000)[14] [Mayo Clinic registry 1996–1999]	164	164	Similar overall survival and cancer-specific survival in RN and PN groups RN associated with increased risk of proteinuria and new-onset CKD* (RR 3.7)	Single-centre, retrospective study
McKiernan *et al.* (2002)[27] [MSKCC renal cancer database 1989–2000, T1a tumours]	117	173	RN associated with increased risk of development of CKD* (P<0.01) Similar oncological outcomes in RN and PN groups	Single-centre, retrospective study Small number of events prevented multivariate analysis (16 patients developed CKD in RN group)
Huang *et al.* (2006)[30] [MSKCC renal cancer database 1989–2005, T1a tumours, normal baseline SCr]	385	262	26% of patients had eGFR <60 ml/min/1.73 m^2 and 2% had eGFR <45 ml/min/1.73 m^2‡ at baseline In the multivariable analysis, RN was an independent risk factor for new-onset eGFR <60 ml/min/1.73 m^2 at 3 years after surgery	Single-centre, retrospective study
Thompson *et al.* (2008)[43] [Mayo Clinic nephrectomy registry 1989–2003, isolated T1a renal cortical tumours]	358	290	No significant association between RN versus PN and death (RR 1.12, 95% CI 0.80–1.56) In patients aged >65 years (n=327), RN associated with increased risk of death (RR 2.16, 95% CI 1.12–4.19), which persisted after adjustment for SCr levels at baseline	Single-centre, retrospective study Small subset of patients aged <65 years with low rate of events (43 deaths)
Barlow *et al.* (2010)[31] [Columbia Comprehensive Clinical Database of Urologic Oncology 1988–2008]	102	174	Pre-operative CKD stage and RN were independent predictors of worse renal outcomes‡	Single-centre, retrospective study
Yokoyama *et al.* (2011)[32] [Tokyo Medical and Dental University Graduate School 1994–2009]	75	341	4% prevalence of preoperative CKD RN was an independent risk factor for new-onset CKD (eGFR <60 ml/min/1.73 m^2;‡ 37% in RN group versus 11% in PN group)	Single-centre, retrospective study

*SCr level >152.50 μmol/l. ‡Modification in Diet and Renal Disease Study equation. Abbreviations: eGFR, estimated glomerular filtration rate; MSKCC, Memorial Sloan–Kettering Cancer Center; PN, partial nephrectomy; RN, radical nephrectomy; RR, relative risk; SCr, serum creatinine.

2.75–5.32 for eGFR <60 ml/min/1.73m^2; and HR 11.8, 95% CI 6.24–22.4 for eGFR <45 ml/min/1.73 m^2).[30] The finding that partial nephrectomy was associated with improved long-term renal function compared with radical nephrectomy has been validated in several subsequent analyses.[31–33]

Population-based studies

Several retrospective population-based analyses have been carried out to further examine renal outcomes after nephrectomy. In a study of 1,151 patients who underwent radical or partial nephrectomy in Alberta, Canada, in 2002–2007, 10.5% of participants had adverse renal outcomes, including end-stage renal disease (ESRD), urgent dialysis, CKD (defined as eGFR <30 ml/min/1.73 m^2), or rapidly progressive CKD (defined as eGFR <60 ml/min/1.73 m^2 with a decline in eGFR ≥4 ml/min/1.73 m^2 per year) during a mean follow-up duration of 32 months.[34] In addition, radical nephrectomy nearly doubled the risk of adverse renal outcomes when compared with partial nephrectomy (HR 1.75, 95% CI 1.02–2.99).

A study that included all patients (n = 44) who underwent partial nephrectomy for RCC in Iceland in 2000–2010 reported similar findings.[35] These patients were matched to participants who underwent radical nephrectomy according to time of operation, tumour node metastasis stage, and tumour size. In comparison to partial nephrectomy, radical nephrectomy had a detrimental effect on eGFR 6 months after surgery (difference in eGFR of 12.6 ml/min/1.73 m^2, P<0.001) and also increased the risk of new-onset CKD (defined as eGFR <60 ml/min/1.73 m^2; OR 3.07, 95% CI 1.03–9.79, P = 0.04).[35]

In a study of 6,433 patients who underwent partial or radical nephrectomy for T1a RCC in the USA between 1998 and 2005, 840 patients from each group were carefully matched on propensity scores to account for selection biases.[36] Those who underwent radical nephrectomy had a higher rate of new onset CKD than did those who underwent partial nephrectomy (20% versus 11%, HR 1.90, 95% CI 1.48–2.45), and the 5-year freedom from new-onset CKD was estimated to be 82% for radical nephrectomy versus 91% for partial nephrectomy (P<0.001).[36] These population-based studies confirm the protective effect of nephron-sparing surgery versus radical nephrectomy on renal outcomes in patients with T1a RCC.

Given the equivalent oncological outcomes of partial and radical nephrectomy,[8–12] the compelling evidence

Table 2 | Population-based studies and randomized controlled trial examining outcomes after partial versus radical nephrectomy

Study [population]	*n*		Results	Limitations
	PN	RN		
Population-based studies				
Miller *et al.* (2008)[50] [SEER registry data linked with Medicare claims 1991–2002]	763	10,123	PN associated with fewer adverse renal outcomes No difference in cardiovascular outcomes In 2000–2002, PN associated with reduced overall mortality (HR 0.72, 95% CI 0.56–0.92)	Retrospective study All patients aged >65 years
Huang *et al.* (2009)[44] [SEER registry data linked with Medicare claims 1995–2002 T1a tumours]	556	2,547	RN associated with increased overall mortality (HR 1.38, $P<0.01$) and number of post-operative cardiovascular events (HR 1.4, $P<0.05$), but not with cardiovascular death (HR 0.95, $P=0.84$)	Retrospective study All patients aged >65 years No data on perioperative kidney function and comorbidities
Zini *et al.* (2009)[45] [Nine SEER registries 1988–2004, T1a tumours]	2,198	7,611	RN associated with increased overall mortality (HR 1.23, $P=0.001$) and non-cancer-related mortality at 10-year follow-up (31.6% in RN group versus 27.1% in PN group)	Retrospective study No data on perioperative kidney function and comorbidities
Klarenbach *et al.* (2011)[34] [Alberta Kidney Disease Network data set 2002–2007]	230	921	RN associated with increased risk of adverse renal outcomes (HR 1.75, 95% CI 1.02–2.99) Baseline proteinuria a strong risk factor for adverse renal outcomes (HR 2.4, 95% CI 1.47–3.88)	No information on tumour stage
Sun *et al.* (2012)[36] [SEER registry data linked with Medicare claims 1998–2005, T1a tumours]	840	840	In multivariable analysis, RN associated with higher rate of post-operative CKD (HR 1.9, 95% CI 1.48–2.45) and acute kidney injury (HR 1.41, 95% CI 1.12–1.79) No significant difference in risk of end-stage renal disease (HR 1.76, 95% CI 0.97–3.19)	Retrospective study All patients aged >65 years Pre-operative kidney function not reported
Tan *et al.* (2012)[47] [SEER registry data linked with Medicare claims 1992–2007, T1a tumours, patients matched using propensity scores]	1,925	5,213	PN associated with lower risk of death (HR 0.54, 95% CI 0.34–0.85) Patients living close to a PN surgeon were more likely to receive PN, but differential distance did not influence overall mortality	Retrospective study All patients aged >65 years
Smaldone *et al.* (2012)[51] [SEER registry data linked with Medicare claims 1995–2007, T1a tumours]	1,665	3,831	In patients aged 68–85 years, PN associated with survival benefit at 1 year and at 3 years post-surgery Survival benefit of PN decreased with time (little benefit observed at 5 years and at 10 years after surgery)	Retrospective study All patients aged >65 years Data not adjusted for comorbidities
Kim *et al.* (2012)[52] [Meta-analysis of 36 studies published in English between 1990 and 2011]	9,281	31,729	PN correlated with a 19% reduction in risk of all-cause mortality (HR 0.81, $P<0.0001$), a 29% reduction in cancer-specific mortality (HR 0.71, $P<0.001$), and a 61% reduction in risk of severe CKD (HR 0.39, $P<0.0001$)	Included 35 retrospective studies and only one randomized clinical trial Substantial study heterogeneity
Mariusdottir *et al.* (2013)[35] [Icelandic Cancer Registry 2000–2010, patients in PN and RN groups matched 1:1 according to time of operation, tumour node metastasis stage, and tumour size]	44	44	RN associated with a higher mean reduction in eGFR and an increased risk of new-onset CKD 6 months after surgery (eGFR <60 ml/min/1.73 m^{2*}, OR 3.07, 95% CI 1.03–9.79) RN associated with higher mortality (5-year overall survival 65% in RN group versus 100% in PN group)	Retrospective study
Shuch *et al.* (2013)[46] [SEER registry data linked with Medicare claims 1992–2007 T1a tumours]	1,471	4,299	PN associated with higher overall survival (median of 10.45 years) compared with matched controls (medians of 8.75 years for bladder cancer controls and 8.76 years for noncancer controls, $P<0.001$) No survival benefits observed for RN	Retrospective study All patients aged >66 years
Randomized prospective clinical trial				
Van Poppel *et al.* (2011)[53] [EORTC-GU multinational, noninferiority phase 3 trial 1992–2003, isolated tumours <5 cm diameter]	268	273	In the intention-to-treat analysis, PN associated with an increased risk of mortality (HR 1.5, 95% CI 1.03–2.16) and a slightly higher rate of cardiovascular deaths (9.3% versus 7.3% in the RN group) No significant differences in mortality after PN or RN in patients with localized renal cell carcinomas <5 cm ($n=195$ per group)	Study closed prematurely due to poor accrual No hard conclusions because of small number of events and high crossover rate Kidney function outcomes not assessed Tumour size limit <5 cm instead of <4 cm (based on data available at time of study design)

*Modification in Diet and Renal Disease Study equation. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EORTC-GU, European Organization for Research and Treatment of Cancer Genito-Urinary Group; HR, hazard ratio; PN, partial nephrectomy; RN, radical nephrectomy; SEER, Surveillance, Epidemiology and End Results; SCr, serum creatinine.

described above supports the current recommendation that partial nephrectomy should be the standard of care for T1a RCC, and a viable option for T1b RCC.[15,16] This strategy might preserve renal function and avoid the potential sequelae associated with development of CKD.

Nephrectomy and cardiovascular outcomes

More than half of RCCs are discovered in the early stages by incidental abdominal imaging[37] and the majority of patients with stage I RCC are expected to remain free of recurrence and metastasis for >5 years after surgical

resection.[13,14] Radical nephrectomy might control the tumour, but also increases the risk of CKD after surgery. The longer the patient is free of cancer, the higher their risk of developing CKD and its associated adverse outcomes, particularly cardiovascular disease.

The adverse impact of declining renal function on cardiovascular events was illustrated by researchers who estimated longitudinal eGFR in >1 million patients in the USA with advanced CKD who progressed to dialysis or kidney transplantation between 1996 and 2000.[38] This retrospective cohort study, which had a median follow-up duration of ~3 years, was one of the first to demonstrate that risk of cardiovascular events increased with a decline in eGFR. Patients with CKD and eGFR <60 ml/min/1.73 m^2 had higher risks of cardiovascular events (HR 1.4, 95% CI 1.4–1.5) and of all-cause death (HR 1.2, 95% CI 1.1–1.2) than individuals with normal renal function. These risks were even higher in patients whose eGFR declined to <30 ml/min/1.73 m^2 (HR 2.8, 95% CI 2.6–2.9 and HR 3.2, 95% CI 3.1–3.4 for cardiovascular events and all-cause death, respectively).[38] On the basis of these data and additional evidence, CKD is now deemed to be an independent risk factor for cardiovascular disease.[39–41]

Retrospective studies

As CKD is a risk factor for cardiovascular disease, the benefits of nephron-sparing surgery might extend beyond preservation of renal function. Systemic morbidities downstream of CKD after nephrectomy might lead to less-favourable survival outcomes.[42] However, the evidence for this association remains inconclusive and controversial, and the potential causal association between nephrectomy and long-term CKD-associated morbidity and mortality is uncertain. In a single-centre cohort of 648 patients who had unilateral, solitary, localized renal masses ≥4 cm and normal renal function at baseline, radical nephrectomy was associated with a significantly higher overall mortality than was partial nephrectomy (relative risk [RR] 2.16, $P = 0.02$) in patients <65 years of age.[43] However, the difference in mortality between the two patient groups was not significant for the entire cohort, highlighting the heterogeneity of the long-term impact of this type of surgery and its interaction with age at the time of operation.[43]

Using data from the Surveillance, Epidemiology and End Results (SEER) cancer registry linked with Medicare claims, the outcomes in 2,991 patients aged ≥65 years of age who underwent radical or partial nephrectomy for T1a RCC between 1995 and 2002 have been analysed.[44] After adjusting for preoperative demographic and comorbid variables, radical nephrectomy was associated with an increased risk of overall mortality compared with partial nephrectomy (HR 1.38, $P < 0.01$). Radical nephrectomy was also associated with increased risks of cardiovascular events (probabilities of freedom of 86% at 3 years and 82% at 5 years in the partial nephrectomy group, compared with 82% at 3 years and 75% at 3 years in the radical nephrectomy group), and cardiovascular death (4.9% in the partial nephrectomy group versus 6.0% in the radical nephrectomy group). However, no significant difference was observed in time to cardiovascular event. Similarly, a study of 1988–2004 SEER registry data from 9,809 patients with T1a RCC showed that radical nephrectomy compared with partial nephrectomy, was associated with significantly increased overall mortality and non-cancer-related mortality at median follow-ups of 35 months and 46 months, respectively.[45] Radical nephrectomy resulted in an estimated absolute increase in non-cancer-related mortality of 4.6% at 5 years and 4.5% at 10 years after surgery.[45]

Statistical adjustment approaches

In an attempt to overcome the potential selection bias and confounding inherent to observational study designs, several SEER–Medicare linked cohorts of patients with T1a RCC have been re-examined using various statistical adjustment approaches. One such study used a greedy algorithm to match patients with localized RCC with control individuals (either without cancer or with non-muscle-invasive bladder cancer) based on demographics and comorbidities.[46] Median overall survival was longer in the partial nephrectomy group (10.45 years) than in matched control groups (8.75 years in the bladder cancer group and 8.76 years in the non-cancer group, $P < 0.001$). However, these survival benefits were not observed for radical nephrectomy.[46] A study that used differential distance between the patient's residence and a partial nephrectomy physician as an instrumental variable (one of the most rigorous statistical methods used to date) reported that partial nephrectomy was associated with a significantly lower risk of overall mortality than radical nephrectomy (HR 0.54, 95% CI 0.34–0.85) and was not inferior in terms of kidney cancer-specific survival (HR 0.82, 95% CI 0.19–3.49).[47]

Propensity score adjustment has also been increasingly used by several groups of investigators. A propensity score estimates the probability of receiving either radical or partial nephrectomy, conditional on known and measurable demographic and disease-specific characteristics, to limit the influence of selection bias and confounding on treatment outcomes.[48,49] In a subgroup analysis of 2000–2002 data (4,422 and 438 patients with radical and partial nephrectomy, respectively, in the USA), partial nephrectomy was associated with a reduced risk of death from any cause (adjusted HR 0.72, 95% CI 0.56–0.92), but no association was observed between surgery type and postoperative cardiovascular morbidity.[50]

The reported survival benefit associated with partial nephrectomy was challenged by a study of patients older than 66 years with T1a RCC who underwent either partial ($n = 1,665$) or radical nephrectomy ($n = 3,831$) from 1995–2007.[51] After adjustment using propensity-score-based weighting, a survival benefit of partial versus radical nephrectomy was observed at 1 year and at 3 years after surgery. However, this survival benefit decreased with time and little survival benefit of partial versus radical nephrectomy was observed >5 years after surgery.[51]

Meta-analysis

A meta-analysis, which included 39 studies and 41,010 patients who underwent nephrectomy for localized renal tumours (77% radical nephrectomy and 23% partial

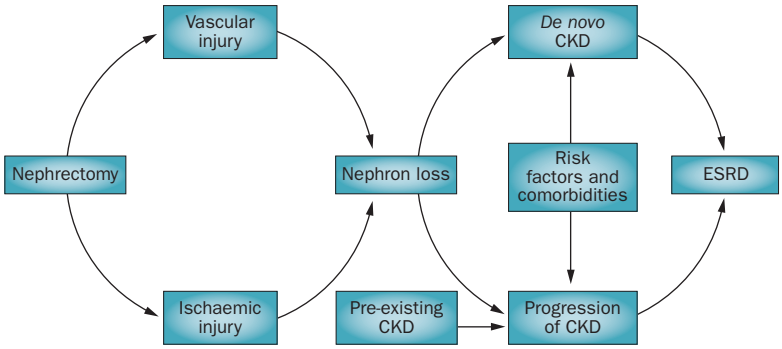

Figure 1 | Potential pathophysiology of *de novo* CKD and progression of pre-existing CKD after kidney tumour nephrectomy. Vascular and ischaemic injury resulting from nephrectomy can lead to nephron loss, which, in combination with risk factors and comorbidities, might result in *de novo* CKD or progression of pre-existing CKD. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease.

nephrectomy), showed that partial versus radical nephrectomy resulted in a 19% reduction in risk of all-cause mortality (HR 0.81, $P<0.0001$). However, the investigators acknowledge that their analysis was limited by substantial heterogeneity in study populations and the use of historical cohorts in the majority of the included studies.[52]

EORTC trial

The debate regarding long-term non-oncological morbidity and mortality after nephrectomy for small renal tumours was fuelled by the controversial European Organisation for Research and Treatment of Cancer (EORTC) trial[53]—the only randomized clinical trial of partial versus radical nephrectomy conducted to date. In this study, 541 patients who had solitary renal lesions with a diameter ≤5 cm and a normal contralateral kidney were randomly assigned to receive either partial or radical nephrectomy. Unfortunately, the trial was closed prematurely because of poor accrual and was limited by high crossover between the treatment groups.

In contrast to observational data, results from the EORTC trial showed more-favourable outcomes in patients treated with radical nephrectomy than in those who underwent partial nephrectomy.[53] During a median follow-up of 9.3 years, 25% of patients who underwent partial nephrectomy and 18.3% of those who underwent radical nephrectomy died. The leading cause of death was cardiovascular disease. The intention-to-treat analysis showed improved outcomes in the radical nephrectomy group with a 10-year overall survival rate of 81.1% compared with 75.5% in the partial nephrectomy group (HR 1.5, 95% CI 1.03–2.16). Interestingly, a subgroup analysis of the EORTC trial showed that partial nephrectomy compared with radical nephrectomy was associated with a 21% reduction in the absolute risk of moderate renal dysfunction (eGFR <60 ml/min/1.73 m^2) during a median follow-up of 6.7 years (absolute risk of 64.7% versus 85.7%, 95% CI 13.8–28.3).[54] The outcome of advanced CKD (eGFR <30 ml/min/1.73 m^2) was reached by 10.0% of patients who underwent radical nephrectomy and 6.3% of patients who underwent partial nephrectomy (difference of 3.7%, 95% CI –1.0 to 8.5).

The finding that partial nephrectomy compared with radical nephrectomy is associated with an increase in mortality, but a decrease in risk of CKD, suggests that moderate renal dysfunction arising from surgery might not have the same negative impact on overall mortality as does CKD arising from medical causes, such as diabetes or hypertension. Similar conclusions were reached by the authors of a retrospective study that included 4,180 US patients who underwent nephrectomy for suspected cancer between 1999 and 2008. Before surgery, 28% of these patients had CKD (GFR <60 ml/min/1.73 m^2) attributed to medical causes, whereas 22% of patients had CKD only after surgery.[55] Surgically induced CKD and postoperative GFR were not significant predictors of overall survival in those patients who did not have CKD before surgery. The EORTC trial is largely considered to be flawed because of the accrual difficulties, premature closure, and high crossover between the treatment groups. Nevertheless, as the likelihood of additional large prospective clinical studies of partial versus radical nephrectomy is low, this randomized trial is valuable and highlights the complexity and tremendous challenges faced when attempting to elucidate the potential relative long-term morbidity and mortality benefits of partial nephrectomy.

Risk factors for CKD after nephrectomy

The same intrinsic kidney risk factors and systemic comorbidities might predispose patients toward developing renal tumours and CKD.[23,24] These factors include baseline demographics (such as age, gender and ethnicity), environmental factors and habits (such as nutrition, smoking status and lifestyle), genetic factors (such as *APOL1* variants), comorbid conditions (such as metabolic syndrome, diabetes mellitus, hypertension, and other acute or chronic disease states) and pre-existing abnormalities in the non-neoplastic kidney parenchyma. In the MSKCC study, 26% of patients with RCC had CKD and eGFR <60 ml/min/1.73 m^2 before surgery despite normal preoperative serum creatinine levels.[30] Hyperfiltration injury to the remaining glomeruli after partial or radical nephrectomy might further predispose patients with RCC to adverse long-term renal outcomes. The subsequent decline in kidney function might be more pronounced if subclinical intrinsic renal abnormalities were present before nephrectomy.[34] Furthermore, lifestyle, demographic, and genetic factors as well as comorbid conditions might have a role in increasing the risk of CKD, or accelerating the rate of progression of pre-existing CKD, after partial or total nephrectomy (Figure 1, Table 3).

Renal parenchymal abnormalities

Pathologic studies have established that glomerular disease or arterionephrosclerosis frequently coexist with RCC.[56–58] Researchers that evaluated non-neoplastic renal parenchyma in resected tumour specimens reported that only 10% of 110 consecutive tumour nephrectomy specimens had completely normal adjacent renal tissue. Clinically significant intrinsic renal abnormalities, including diabetic nephropathy, glomerular

Table 3 | Risk factors associated with CKD after cancer nephrectomy

Risk factor	*De novo* CKD	Acceleration of pre-existing CKD
Nephron loss		
Partial versus radical nephrectomy	+	++
Demographics		
Age	+	+
Gender	?	?
Ethnicity*	++	++
Environmental factors		
Smoking	?	?
Nutrition and diet (high intake of protein and salt)	+	++
Genetic factors		
APOL1 gene	++	++
Other candidate genes	?	?
Comorbid conditions		
Metabolic syndrome and obesity	++	++
Diabetes mellitus	+++	+++
Hypertension	++	+++
Cardiovascular diseases	+	+
Other comorbidities	?	?
Pre-existing renal factors		
Microalbuminuria and proteinuria	++	++
Haematuria	?	?
Low glomerular filtration rate	++	+++
Glomerular and interstitial diseases	+++	+++
Pre-renal states and cardiorenal syndrome[104]	?	+
Obstructive conditions	+	+
History of acute kidney injury	++	+++
Kidney histopathology		
Malignant tissue histopathology	?	?
Nonmalignant tissue histology	++	++
Other factors		
Perioperative events	+	+
Surgical technique	+/−	+/−

*Risk of *de novo* CKD or CKD progression after nephrectomy might be higher in black or Hispanic patients than in white patients.[105] Abbreviations: CKD, chronic kidney disease; +, likely association; ++, highly likely association; +++, very highly likely association; +/−, unknown association; ?, questionable association.

hypertrophy, mesangial expansion, and diffuse glomerulosclerosis were evident in >60% of the remaining samples.[56] These findings prompted the College of American Pathologists to update the protocol for examination of tumour nephrectomy and nephroureterectomy specimens, effective since January 2010, to require routine evaluation of non-neoplastic renal parenchyma.[59]

In a study of 110 consecutive tumour nephrectomy specimens, patients with clinically significant renal parenchymal abnormalities showed a greater decline in serum creatinine levels at 6-month follow-up than those who had normal tissue adjacent to their tumour (97.24 ± 159.12 μmol/l versus 17.68 ± 17.68 μmol/l, $P = 0.01$).[56] However, the study was limited by the small number of available follow-up serum creatinine measurements. Among 156 patients who were followed-up for a minimum of 12 months after tumour nephrectomy, the presence of severe arteriosclerosis or arteriolosclerosis, >10% interstitial fibrosis or tubular atrophy, or >5% glomerulosclerosis in nephrectomy specimens were risk factors for significantly higher postoperative serum creatinine levels.[58] Furthermore, elevation of postoperative serum creatinine was much higher following radical nephrectomy than following partial nephrectomy given the same degree of these pre-existing parenchymal pathologic changes. Using eGFR, several other studies have reported similar associations between renal function outcomes and underlying histopathologic abnormalities evident in non-neoplastic renal parenchyma. In a study that included 150 patients with a median follow-up of 15 months, the presence of arteriosclerosis was an independent predictor of the percentage decline in eGFR after laparoscopic partial nephrectomy.[60] By contrast, a study with longer follow-up duration (mean 19.7 months) showed that percentage change in eGFR after laparoscopic radical nephrectomy was significantly associated with the extent of glomerulosclerosis ($P = 0.034$) but not with the extent of arteriosclerosis or the presence of interstitial fibrosis.[61] For each 10% increase in glomerulosclerosis, eGFR after surgery decreased by 9% from baseline.

Comorbidities

Pre-existing comorbidities might also compromise renal function after nephrectomy as a result of their long-term effects on the remnant renal parenchyma. Unsurprisingly, age, diabetes, hypertension, and tobacco use are independently associated with the development of CKD after nephrectomy for RCC, as well as with renal insufficiency (defined as elevated serum creatinine levels or reduced eGFR before surgery) in the general population.[31,33,34,62,63] Significantly higher rates of proteinuria, which confers an additional risk of CKD or cardiovascular disease, have also been reported in patients who have undergone radical nephrectomy compared with those who have undergone partial nephrectomy.[14,34,63,64]

Preserved renal function

Preservation of renal parenchyma by partial nephrectomy is the most-likely mechanism for its observed advantage over radical nephrectomy in preventing CKD in patients with small renal tumours. Larger preserved renal volume, or functional volume, is an independent predictor of better renal function outcome among patients with a solitary kidney who have undergone partial nephrectomy.[65–67] A 5% increase in the amount of preserved kidney has been estimated to correlate with a 17% reduction in the risk of *de novo* stage 4 CKD.[67] The integrity of the preserved parenchyma after partial nephrectomy is as predictive of risk of CKD as is the quantity. In a study that included 1,169 patients, each additional minute of warm ischaemia beyond 20 min during open or laparoscopic partial nephrectomy was associated with slightly greater renal impairment.[68] The impact of warm ischaemia on the quantity and quality of preserved kidney was

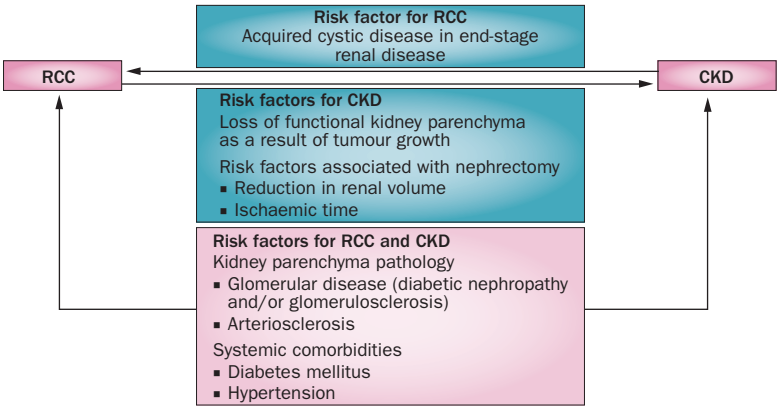

Figure 2 | Potential bidirectional relationship between RCC and CKD. Intrinsic kidney pathology and systemic comorbidities are shared risk factors that can predispose toward both RCC and CKD. Acquired cystic disease in non-functioning kidneys in end-stage renal disease can lead to RCC. Conversely, tumour expansion and surgery-related risk factors in the setting of RCC can lead to CKD. Abbreviations: CKD, chronic kidney disease; RCC, renal cell carcinoma.

reflected by the decline in renal function immediately after the surgery. The degree of nadir eGFR reduction was associated with ultimate progression to CKD after adjusting for other risk factors.[68] A warm ischaemic time >25 min was previously shown to more than double the risk of severe CKD.[69] Interestingly, a study has shown that even if ischaemic time during partial nephrectomy is prolonged (>30 min) renal function outcomes are superior to those after radical nephrectomy.[70]

Thermal ablation techniques, including radiofrequency ablation and cryoablation, are alternative minimally invasive nephron-sparing treatments for small renal lesions. These techniques, which can be performed using a percutaneous or laparoscopic approach, do not require dissection and clamping of the renal hilum and, therefore, confer minimal ischaemic insult.[71] Although promising, the oncological and renal efficacy of thermal ablation in comparison with partial nephrectomy have yet to be established because of small sample sizes and lack of long-term follow-up data among existing studies.[72–77] Thermal ablation techniques and active surveillance (the most minimally invasive approach) are often reserved for patients who are elderly or comorbidly ill.[78]

Limitations of existing studies

Compelling evidence supports a protective benefit of partial versus radical nephrectomy in terms of development of CKD. Preservation of kidney tissue in patients with RCC should, therefore, be a priority when possible. However, the majority of this evidence comes from single-centre cohort studies that lacked a standardized definition of renal impairment (measurements used included absolute serum creatinine levels, creatinine-based eGFR equations, and radioactive markers) and used various cutoff points of eGFR levels and stages of CKD stage as the primary outcomes. In addition to disparities between inclusion and exclusion criteria, large variability exists in duration of follow-up, which was as short as 3 months after surgery in some studies. The population-based studies had larger sample sizes and longer follow-up times. However, as the included data were obtained from cancer registries and the SEER database, the designations of CKD, cardiovascular events, and causes of deaths were extracted based on diagnostic or administrative codes and Medicare insurance claims. The results obtained depended largely on the accuracy of the coding and no actual measurements of renal function were available. In addition, as mentioned above, the EORTC trial is considered to be flawed because of premature closure and high crossover rates between the treatment groups.

ESRD is the definitive adverse renal outcome and is associated with significantly increased risks of cardiovascular morbidity and mortality. A 60-year old patient with ESRD is estimated to survive for only 4.6 years on dialysis compared with 21 years for an average person of the same age not on dialysis.[79] Cardiovascular disease accounts for >50% of deaths in the ESRD population.[80] ESRD is, therefore, a significant public health burden. The Medicare expenditure for renal replacement therapy and its associated complications rose to nearly US$33 billion in 2010, nearly double compared with the previous decade.[81] However, none of the studies mentioned above designated ESRD after nephrectomy as a primary end point. In a Canadian cohort of 1,151 patients with renal lesions undergoing nephrectomy, 2% of patients developed ESRD or required dialysis during a median follow-up of 32 months.[34] Due to the low incidence, ESRD was examined only as part of a composite renal outcome. Similarly, in the MSKCC series, none of the participants needed acute or chronic renal replacement therapy.[27] In a SEER–Medicare linked cohort from 1988 to 2005, 4% of patients who underwent radical nephrectomy and 2% of patients who underwent partial nephrectomy had developed ESRD at the end of 2008. However, the difference in risk of ESRD between the treatment groups failed to achieve statistical significance.[36] In the subgroup analysis of the EORTC trial, the incidences of ESRD in patients who underwent radical nephrectomy and in those who underwent partial nephrectomy were nearly identical (1.5% versus 1.6%).[54] Controversy remains regarding the potential benefits of partial versus radical nephrectomy for small renal masses, especially the long-term survival benefits and ultimate renal outcome of ESRD—further research is needed.

Future research

Advanced CKD or ESRD and acquired cystic kidney disease (ACKD) are risk factors for RCC. An association between RCC and ESRD with ACKD in patients on haemodialysis was first reported in 1977.[82] Compelling evidence has since confirmed that patients with ESRD have a higher risk of developing RCC than do the general population.[83–87] Duration of dialysis has been associated with ACKD, which is an important risk factor for RCC.[88–92] RCC might also develop in the native kidneys of renal transplant recipients, even in those who have good graft function.[93–96] RCC that arise from the native kidneys of patients with ESRD or kidney transplant recipients are detected at a younger age, are of smaller size, are less likely to be symptomatic, and have less metastatic potential

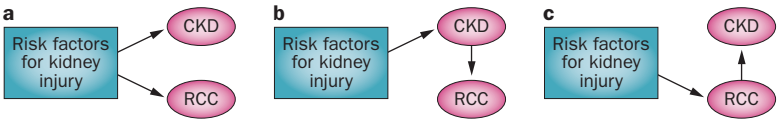

Figure 3 | Hypothetical causal models for the association between cancer nephrectomy for RCC and increased risk of CKD. **a** | Factors that increase the risk of kidney injury are associated with both CKD and RCC but these outcomes are unrelated. **b** | Factors that increase the risk of kidney injury are associated with the development of CKD, which in turn increases the risk of RCC. **c** | Factors that increase the risk of kidney injury are associated with the development of RCC, which in turn increases the risk of CKD. Abbreviations: CKD, chronic kidney disease; RCC, renal cell carcinoma.

than sporadic RCCs.[97] They also had a wide spectrum of distinct pathologic features and prevalence that varies by dialysis vintage, with ACKD-associated RCC being most common in patients who have been on dialysis for ≥10 years.[98] However, the exact pathophysiology by which the uraemic state, dialysis, and transplantation can cause malignant transformation in the kidney remains unknown and is likely multifactorial.[99] Future research should be extended to examine the long-term impact of nephrectomy on the development of ESRD as a primary end point, and the potential bidirectional (Figure 2) and causal relationships (Figure 3) between RCC and CKD. The use of population-based dialysis databases with long follow-up durations, frequent patient visits and evaluations, and longitudinal measures of renal and cardiovascular outcomes and their associated risk factors might provide a unique opportunity to answer these questions by comparing patients with ESRD and RCC to carefully matched patients who have ESRD without RCC.

More research is also needed to improve understanding of the pathophysiology of risk of CKD after nephrectomy and to quantify the perioperative risks and long-term benefits of nephron-sparing surgery and the role of other factors, such as pre-existing comorbidities and parenchymal renal diseases, in preventing new-onset CKD or slowing the rate of progression of pre-existing CKD. The development and validation of a prediction model (incorporating demographic and environmental factors, blood and urine indices, imaging studies, and histopathologic changes in malignant and nonmalignant tissue) to identify patients who are at risk of increased short-term and long-term oncological and non-oncological morbidity and mortality after nephrectomy is urgently needed. Such a model would help guide follow-up care after surgery or trigger discussion of alternative management options such as active surveillance or laparoscopic ablation.

Conclusions

Given the oncological equivalence of partial versus radical nephrectomy for stage I RCC, the current emphasis of clinical management has shifted to preserving renal parenchyma to prevent development of postoperative CKD and its associated morbidity and mortality. However, despite strong evidence supporting partial nephrectomy as the standard of care for T1a RCC and a viable option for T1b tumours, this approach has been underutilized, with reported rates of <50% in the USA in 2006[100] and only 4% in England in 2002.[101] Its use is highly clustered around experienced tertiary care centres, and partial nephrectomy is most likely to be offered to young male patients with small tumours.[100]

Despite advances in surgical techniques, partial nephrectomy remains a challenging operation and is associated with a higher rate of adverse outcomes than is radical nephrectomy.[102] A complication risk of ≥20% has been reported for partial nephrectomy of renal masses of moderate and high complexity.[102,103] In addition, ongoing controversy and debate exists regarding the long-term cardiovascular and survival benefits of partial nephrectomy as a result of the inherent selection bias in retrospective observational studies and the lack of data from prospective clinical trials. Indeed, results from the only existing randomized trial, which had many limitations, increased the controversy. The decision whether or not to recommend nephron-sparing surgery for patients with small renal masses should, therefore, be made on an individual basis after thorough evaluation of comorbidities and risk factors, in particular the existence of baseline renal insufficiency. The surgery must also be carefully planned to include estimates of parenchymal volume reduction and to minimize intraoperative ischaemic time. Given the substantial burden of CKD and ESRD, a great need exists for research on *de novo* and accelerated CKD and ESRD after nephrectomy, and the bidirectional relationship between RCC and CKD to prevent progression to these ultimate adverse renal outcomes.

Review criteria

A search for original articles published between January 1969 and October 2013 focusing on nephrectomy, RCC, and CKD was performed in MEDLINE and PubMed. The search terms used were "nephrectomy", "RCC", and "CKD", alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for additional relevant papers.

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